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Articles

Molecular pathology of cyclooxygenase-2 in neoplasia

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Cyclooxygenase (COX)-2 levels are elevated in several types of human cancer tissues. Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit both the COX-1 and COX-2 protein, the two enzymes that convert arachidonic acids to prostaglandins. Regular use of such NSAIDs significantly reduces the risk and spread of some cancers. The objective of this study was to elucidate the molecular pathology of neoplasms that overexpress COX-2. Epidemiological data and clinical studies were analyzed and compared with results of studies of human tumor tissues, animal models, and cultured tumor cells. COX-2, but not COX-1, is highly expressed in human colon carcinoma, squamous cell carcinoma of the esophagus, and skin cancer. COX-2 is inducible by oncogenes ras and scr, interleukin-1, hypoxia, benzo[a]pyrene, ultraviolet light, epidermal growth factor, transforming growth factor beta, and tumor necrosis factor alpha. Dexamethasone, antioxidants, and tumor-suppressor protein p53 suppress COX-2 expression. COX-2 synthesizes prostaglandin E2 (PGE2) which stimulates bcl-2 and inhibits apoptosis, and induces interleukin-6 (IL-6) which enhances haptoglobin synthesis. PGE2 is associated with tumor metastases, IL-6 with cancer cell invasion, and haptoglobin with implantation and angiogenesis. Drastic reduction in polyp number results from COX-2 gene knockout as well as from selective COX-2 inhibition in a mouse model of human familial adenomatous polyposis. Nonselective NSAIDs, for instance aspirin, and selective COX-2 inhibitors such as celecoxib (SC-58635) and NS-398 suppress azoxymethane-induced colon carcinogenesis in rats. Aspirin, indomethacin, and ibuprofen decrease cultured lung cancer cell proliferation. Selective inhibition of COX-2 is preferable to nonselective inhibition. It reduces cancer cell proliferation, induces cancer cell apoptosis, and spares COX-1-induced cytoprotection of the gastrointestinal tract.